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Original Research Paper

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17-β- HYDROXYSTEROID DEHYDROGENASE TYPE 3 DEFICIENCY: CASE REPORT OF A RARE CAUSE OF 46, XY FEMALE PHENOTYPE IN ADULTHOOD

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ABSTRACT

Objective: To review a case of disorder of sexual differentiation (DSD) in an adult female patient and the potential challenges and complexity in diagnosing and managing these conditions.

Methods: We review a case of a 34 year-old 46, XY (+SRY) female presenting with primary amenorrhea, hirsutism and infertility with clinicalcourse leading to her suspected and confirmed diagnosis.

Results: A 34-year-old 46, XY (+SRY) female presented with primary infertility after 12 years of marriage. at age21. Based on her clinical presentation and investigations, she was found to have 17-β-HSD3 deficiency due to a homozygous mutation in the HSD17B3 gene. Molecular confirmation of her condition, provided her a more accurate and individualized treatment plan as well as personal risk assessment for her family members.

Conclusion: 17-β-HSD3 deficiency is reported to be a rare cause of female 46, XY DSD but may be overlooked in adult patients due to clinical similarities with androgen insensitivity and lack of genetic testing in suspected cases. It is essential to have a multidisciplinary team to help confirm the diagnosis and provide comprehensive care to affected individuals

KEYWORDS : Disorder Of Sexual Differentiation, Androstenedione, 17-β-hydroxysteroid Dehydrogenase Type 3

INTRODUCTION

Disorder of sexual differentiation (DSD) include a variety of conditions resulting in discordance among the genotypic, gonadal and phenotypic sex of an individual. While many cases are identified at birth due to the presence of ambiguous genitalia, others may present at the time of puberty with few diagnosed later into adulthood. We present a case of a 46, XY female who initially presented with primary infertility at age 34 and review the diagnostic criteria for 17-β-hydroxysteroid dehydrogenase type 3(17-β-HSD3) deficiency, a reportedly rare but suspected overlooked cause of female 46, XY DSD.

CASE STUDY

In the present study, A 34 year-old female presented to endocrinologist for primary infertility. She had never attained menarche and she was investigated by gynaecologist for primary infertility after 12 years of marriage with no obvious cause found.. Her pubertal history was notable for minimal breast development and the presence of normal female appearing axillary and pubic hair. She had a normal growth history with a final adult height of 5 feet 5 inches. She additionally noted intermittent lower abdominal pain and hirsutism. She had been sexually active after marriage . Her physical exam was notable for Tanner 2 breast development, a short vaginal pouch and clitoromegaly with a clitoral width of 1.5 cm and length of 7.7cm.As part of her evaluation, a transvaginal ultrasound was performed, which was notable for the presence of bilateral inguinal gonads without internal female structures. A karyotype revealed that she was 46, XY (+SRY). She was initially referred to gynecology, where initial laboratory testing included a morning total testosterone of 296 ng/dL, estradiol of 21pg/mL, , LH of 18.1mIU/mL and FSH of 11.7 mIU/mL. She was subsequently referred to endocrine clinic for further evaluation, at which time she noted deepening of her voice, hirsutism without a history of hair loss, acne, or known electrolyte or blood pressure abnormalities. She had no known family history of chromosomal abnormalities, inherited disorders, infertility, or consanguinity. Additional biochemistry and endocrine evaluation was performed.

DISCUSSION

The overall incidence of 46, XY DSD is estimated to be 1 in 20,000 births [2]. Most cases of female 46, XY DSD are due to androgen in sensitivity syndromes (AIS), either complete or partial AIS, or gonadal dysgenesis, with enzyme deficiencies comprising the remainder of the cases. A recent review out of Denmark noted the estimated incidence of AIS to be 1–5 in 100,000 births and gonadal dysgenesis 1 in 80,000 births [3]. The incidence of 17-β-HSD3 deficiency is not as well established, however, with estimates varying widely—from 1 in 200–300 to 1 in 147,000 live births–depending on the presence of consanguinity within the population or high carrier frequency rates [4,5]. Inheritance is autosomal recessive and due to compound heterozygous or homozygous mutations in the HSD17B3 gene located on chromosome 9q22.32, with up to 40 pathogenic variants reported [1,5,6]. This is in contrast to the more common condition of AIS, which is inherited in an X-linked pattern due to mutations in the AR gene [7]. Loss of function gene mutations in the HSD17B3 gene affect androgen synthesis in the Leydig cells of testes, where the isoenzyme 17- β-HSD3 converts androstenedione to the more active androgen, testosterone [6]. In infancy, affected individuals often present with female appearing external genital with minimal virilization, a blind vaginal pouch, inguinal testes, and hypoplastic or absent prostate, resulting in female gender assignment [8].

Internal female structures are not present due to the presence of anti-mullerian hormone by the functioning testes, which typically is realized later in life. The condition usually comes to medical attention at the time of puberty due to increased virilization of the external genitalia secondary to peripheral conversion of and rostenedione to testosterone by extra gonadal 17-β-HSD enzymes, including 17β-HSD-5, or due to partial activity of 17-β-HSD3 [6]. Some individuals who had been raised as females may identify as male postpuberty [8]. Those with 17-β-HSD3 deficiency may be clinically

indistinguishable from other causes of female 46, XY DSD, including androgen resistance syndromes or other disorders of testosterone biosynthesis, including 5 alpha-reductase type 2 deficiency, due to the wide range of phenotypes seen with these conditions. The overall Given the potential for clinical ambiguity, high index of suspicion and laboratory evaluation is crucial for diagnosis with genetic testing required as confirmation. Typically, affected individuals will have an elevated androstenedione concentration compared to testosterone and a ratio of testosterone to androstenedione (T/A) of less than 0.8 [4,5]. Pre-puberty, -HCG stimulation testing may be required to achieve a fully stimulated androstenedione concentration given other conditions may also present with a low T/A ratio, including Leydig cell hypoplasia or testicular dysgenesis; however, it is important to be aware that this ratio has been shown to result in both false positive and negative diagnoses and therefore may not always reveal the correct diagnosis [9]. Our patient presented with a testosterone concentration of 1.25 ng/dL and androstenedione concentration of 9.79 ng/dL with a T/A ratio of 0.12. While these results supported the diagnosis of 17- -HSD3 deficiency and not partial AIS, genetic testing was performed to provide a definitive diagnosis. Testing is essential in counseling with regard to the etiology and natural history of her condition, along with for counseling others in her family, in particular those of reproductive age. In conclusion, 17-β-HSD3 deficiency is a rare and suspected under diagnosed cause of 46, XY DSD given its clinical overlap with other more common causes of female 46, XY DSD. Laboratory analysis may help to support the diagnosis, with the presence of a high androstenedione concentration compared to testosterone and subsequent low T/A ratio; however, genetic testing is often required as a confirmation. Genetic counseling should be offered to all affected individuals and management should comprise of a multidisciplinary team to best care for the medical, surgical and psychosocial needs of patients and their families.

CONCLUSIONS

17-β-HSD3 deficiency is reported to be a rare cause of female 46, XY DSD but may be overlooked in adult patients due to clinical similarities with androgen insensitivity and lack of genetic testing in suspected cases. It is essential to have a multidisciplinary team to help confirm the diagnosis and provide comprehensive care to affected individuals

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